HISTOGENESIS OF HEPATIC CIRRHOSIS STUDIED BY THE THREE-DIMENSIONAL APPROACH *

HANS POPPER, M.D., and HANS ELIAS, Ph.D.

From the Hektoen Institute for Medical Research and the Department of Pathology of Cook County Hospital (Dr. Popper) and the Department of Anatomy, Chicago Medical School (Dr. Elias), Chicago, Ill.

The forces that transform a normal liver into a cirrhotic organ are not clearly understood. Many hypotheses have been offered.[1-6] The most acceptable description of cirrhosis is that of an altered reconstruction of the lobular pattern; however, the dynamics of the altered reconstruction are still not fully established. The recent re-examination of the structure of the normal liver based on three-dimensional analysis[7] and a statistico-geometric method[8] suggested the utilization of the same principle in the approach to the study of the cirrhotic liver. In the continuation of investigations devoted to the vascular supply in cirrhosis,[9] the structural alterations of parenchyma and connective tissue have been analyzed. Whether the connective tissue alterations are considered the primary process in cirrhosis[10] or as secondary to parenchymal impairment,[2] these alterations are in the morphologic foreground and received, therefore, the main attention in the study to be reported.

MATERIALS AND METHODS

Necropsy material demonstrating various types of cirrhosis was investigated. The material was fixed in formalin and cut in either single or serial paraffin sections. In addition to routine hematoxylin and eosin stains used primarily for diagnosis, van Gieson's stain with or without nuclear stain was employed. Mallory's aniline blue stain and the silver impregnation method of Gomori were applied also. Single sections, cut in three directions perpendicular to one another, were subjected to statistico-geometric analysis.[8] Reconstruction from serial sections was made with the help of either glass plates[11,12] or wax plates. In some instances models were made by photographing serial sections stained by van Gieson's method without nuclear stain on negative films. Prints were made on lantern slide plates which later were stacked to give an authentic three-dimensional image of the collagenous connective tissue. In this study, collagenous connective

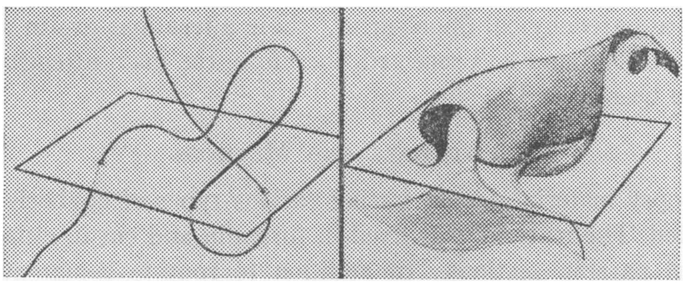
* Supported by grants from the U.S. Public Health Service and from the Dr. Jerome D. Solomon Memorial Research Foundation.

Received for publication, August 9, 1954.

tissue is defined as the material stained red by van Gieson's method. It is not necessarily identical with collagen as defined chemically or with collagen fibers as defined by characteristic periodicity under the electron microscope. Further investigations will have to clarify the relation of argyrophilic (reticulum) fibers to collagenous material.[13,14] The factual observations presented frequently were arrived at by elimination or acceptance of alternate hypotheses. Descriptions of these hypotheses would lengthen this report cumbersomely. Detailed descriptions are therefore presented in a separate study[15] primarily devoted to histo-mechanical considerations of the formation of cirrhosis.

Connective Tissue: General Observations

By the application of statistico-geometric criteria, evidence has been obtained[8] that the collagenous connective tissue in many cases of cirrhosis consists mostly of membranes rather than of fibers. A fiber, as a structure of mainly one dimensional extension, appears in a histologic section as a dot (Text-fig. 1) or as a very short line or



Text-fig. 1. Drawing demonstrating appearance of a fiber or of a membrane in a histologic section.

"comma." The length of the "comma" depends on the angle of inclination between fiber and cutting plane and on the thickness of the section. Short commas and dots are far more numerous than long lines when masses of fibers are sectioned. If long lines prevail in the section, the presence of membranes as predominantly two-dimensional structures, such as a sheet of paper, must be assumed, for almost any plane that intersects a membrane will produce a line. Several membranes may aggregate to form a thicker septum which thus represents a thicker, but still flat, mainly two-dimensional, structure.

Processes Resulting in the Formation of Cirrhosis

Formation of cirrhosis may result from several processes described under the following headings: (1) collapse following massive and submassive necrosis; (2) portal and periportal inflammation; (3) central toxic necrosis; (4) passive congestion; (5) fatty metamorphosis, and (6) pericholangiolitis (inflammation around the smallest bile ducts). In all of the processes, parenchymal nodules eventually form by dissection from the lobular parenchyma. These nodules may be composed of several lobules or of parts of them, as in coarse nodular cirrhosis[1,5]; or the nodules may be parts of one original lobule. The process of the formation of the second type of small nodule will be discussed under portal and periportal inflammation, although it applies to other forms as well.

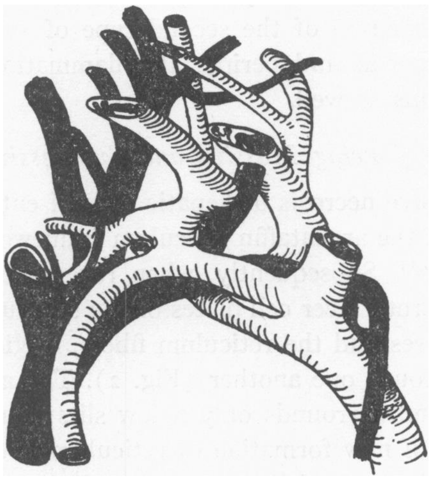
Collapse Following Massive and Submassive Necrosis

Following massive necrosis of hepatic cells of entire liver lobules or groups of lobules, the argentaffin reticulum framework at first remains intact (Fig. 1).[16,17] Subsequently, when regenerating liver cells fail to replace the necrotic liver cell plates or the surrounding exudate, the framework collapses and the reticulum fibers, originally separated by liver cell plates, touch one another (Fig. 2). The argentaffin network appears denser and surrounds only a few slits; but there is no convincing evidence of new formation of reticulum fibers.

Before the collapse, a delicate, slightly fuchsinophilic material is noted between the necrotic liver cells. On high contrast films the material has a fine fibrillar structure (Fig. 3). After the collapse, a few collagenous membranes become visible (Fig. 4). They appear suspended in the meshes of the reticulum fibers and are only exceptionally independent of them. They are without question newly formed connective tissue, although fibroblasts are hardly noted (Fig. 5). The arrangement is similar to that described[18] for the zona glomerulosa of the adrenal cortex.

When entire liver lobules collapse, the portal and hepatic canals become approximated, resulting in relatively large areas of connective tissue, vascularized by some of the old sinusoids (Fig. 6). The portal triads and the central hepatic veins appear in normal arrangement, but the distance between them is considerably shorter than 0.5 mm. which is the average radius of a healthy liver lobule. This is seen in the grossly visible large scars characteristic of the post-necrotic or toxic cirrhosis.[1,5,19-21] Reconstruction of such an area reveals that the normal characteristic interdigitation between the portal and hepatic venous tree[22,23] is maintained (Fig. 7); however, in contrast to the norm, the angle of branching of portal and hepatic vessels becomes sharply acute (Text-fig. 2).

In the collapsed area the preservation of the basic architecture is indicated also by the characteristic difference of the collagenous connective tissue in the collapsed lobule itself, which is membranous in character, from the thick fibers and fibrous bundles of the portal triads and the adventitia of the central veins, which appear on cut sections as dots or commas (Fig. 7).



Text-fig. 2. Reconstruction of portal canals (white) and hepatic canals (black) in a collapsed area after massive necrosis. The approximation of both systems and the acute angulation with maintenance of original interdigitation may be noted. The arch on the bottom was filled out by surviving liver tissue.

This process of massive necrosis and collapse may set in motion other processes. A rapidly collapsing area acts as a partial vacuum[9] and thus exerts centripetal traction upon the surrounding tissue which is not massively necrotic. This results in lines or planes of stress (Fig. 8) which are arranged radially about the area of collapse. Therefore, the liver plates become stretched in the direction of the traction and are consequently flattened transversely. At the same time the reticular framework is distorted but not broken, and the sinusoids are dilated. The liver cells atrophy in this location and disappear. This results in the appearance of a parenchymal fissure. Collagenous membranes develop in the persisting reticulum framework. Numerous membranes developing in a fissure may aggregate to form a septum. This septum traverses the parenchyma surrounding the collapsed area without relation to the lobular architecture. Development of fissures from stress followed by septum formation has been noted also in the livers of pigs.[24]

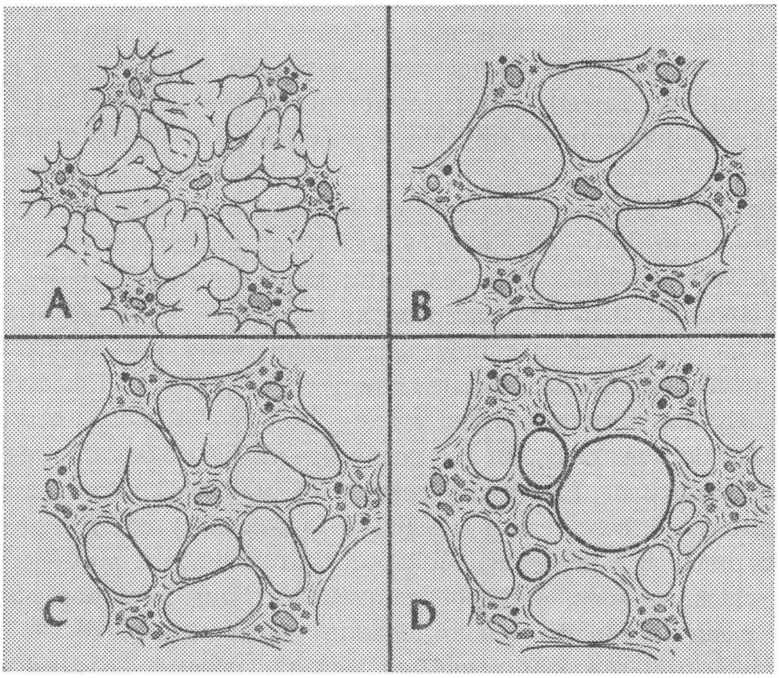
In submassive collapse,[25] only part of a lobule or parts of neighboring lobules become necrotic (Fig. 9). The collapsed portions reveal changes similer to those in massive collapse, whereas the non-necrotic portions are traversed by septa resulting from fissures. Regeneration and re-arrangement of liver cell plates, moreover, produce nodule formation, as will be discussed.

In principle, the process is similar whether massive or submassive necrosis occurs in a previously cirrhotic parenchyma (secondary collapse); however, under these circumstances the approximated central fields and portal triads do not have the normal relationship to each other and the connective tissue membranes of the collapsed area are not sharply differentiated from the fibers of the portal triads and central fields.

Comment. Cirrhosis after collapse following massive or submassive necrosis results from the disappearance of all or many liver cells of one or several lobules. The connective tissue increase in collapse is more apparent than real inasmuch as the fibers of the argentaffin reticulum framework are only approximated and not augmented. Delicate collagenous membranes, however, are perhaps formed from extremely fine fibrillar material (giving "collagen" staining) between the necrotic liver cells. In the connective tissue masses the vessels are approximated. In primary collapse of previously normal tissue, the pattern of these vessels is regular. In secondary collapse of cirrhotic tissue, it is irregular. Collapse itself leads to a post-necrotic scar which, as such, does not represent cirrhosis formation. Such scars occur in syphilis (hepar lobatum) or in atrophy of the left lobe.[26] Several reactions associated with the collapse do cause cirrhosis. The first is the formation of fissures in the non-massive necrotic tissue. In these fissures connective tissue septa form with a few persisting vessels, thus dissecting the lobules also outside the collapsed area. Second, in submassive collapse,[25] lobular fragments form nodules which either had been part of a lobule or, if larger, are composed of several lobules. The smaller the nodules[19-21] and the more acute the necrosis, the more intensive are the regenerative changes (to be discussed). Third, acute necrosis incites portal and periportal inflammation, potentially resulting in septum formation. These three processes are more intense in the rather rapid type of collapse resulting from viral infection or intoxications. The post-necrotic scarring, therefore, in these conditions, usually is associated with cirrhotic changes in the rest of the liver.

Portal and Periportal Inflammation

Various types of inflammation in the portal triads, as produced by bacterial infection, granulomatous or parasitic diseases, iron deposition in hemochromatosis, and possibly also in later stages of viral hepatitis, are associated with increase of collagenous connective tissue in the portal triads and the surrounding periportal area. The inflammation is often associated with destruction of the limiting plate[7] and

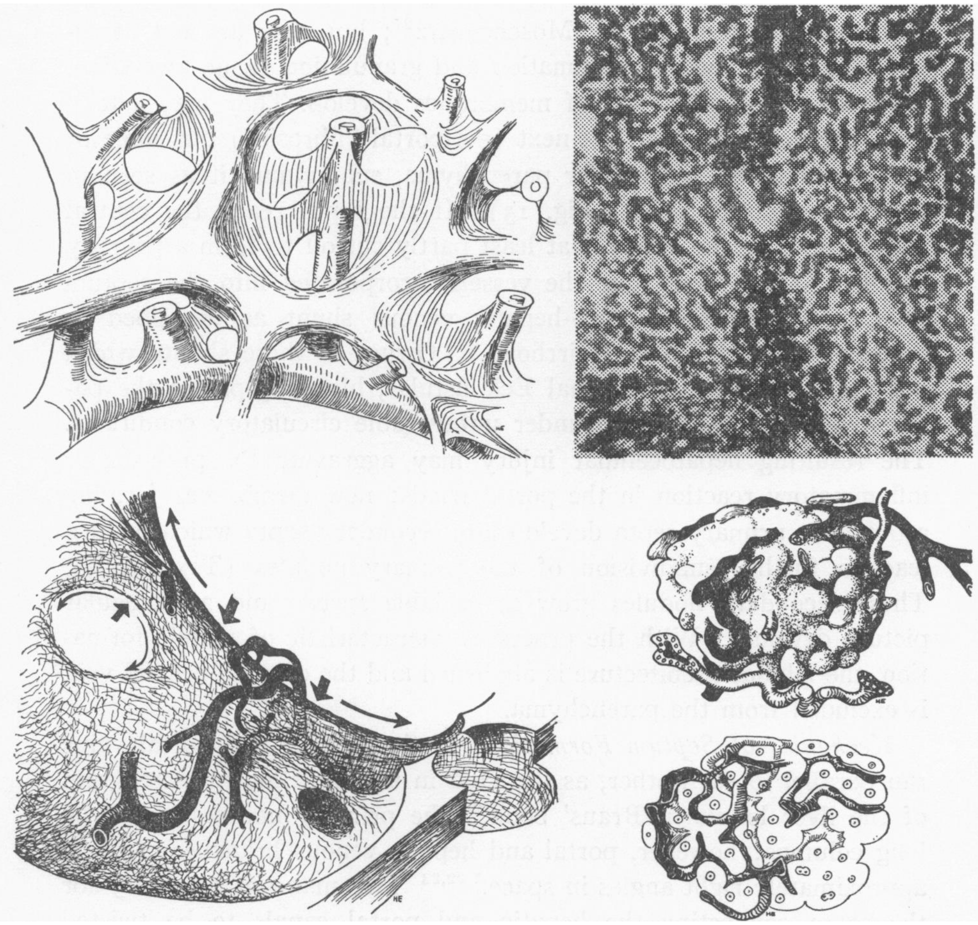


Text-fig. 3. Diagrams of nodule formation by septa. A. Membranes radiating from portal and central fields. B. Membranous tracts aggregate to form septa which subdivide the lobule. (Text-figs. 3A and 3B are reproduced by permission of the Josiah Macy, Jr. Foundation from *Transactions of the 11th Conference on Liver Injury,* 1952, page 181.) C. Further subdivision of lobular fragments (nodules) by septa. D. Regenerating nodules obscure original architecture.

a strand-like infiltration of the periportal area by inflammatory cells (Fig. 10). In early stages this is associated with formation of delicate collagenous membranes found between the liver cell plates radiating from the portal canals (Fig. 11) and acting as reinforcements of the reticulum fiber framework in the tissue space. Membranes develop by adhesion of smallest "micromembranes" (Fig. 12). The membranes finally touch one another when liver cells disappear between them and thus septa are formed which are recognized with low magnification. These septa extend from the portal triads and assume various shapes as seen in three-dimensional reconstruction (Fig. 13).

The septa developed by selection of micromembranes originate in the forks of the portal canals. The sinusoids located in the developing septum become incorporated in it, some of them persisting as blood-carrying channels. They lose their sinusoidal character and become little veins as described by Moschcowitz[27]; but they are not necessarily associated with inflammation and granulation tissue formation. Eventually stronger tracts of membranes develop. They may extend from one portal triad to the next (periportal "fibrosis") but some of them extend into the lobular parenchyma, subdividing it as seen in the reconstructed model (Fig. 13). If the septa reach the central field (Fig. 15), the lobule is at least partly cut off to form a primary nodule. At the same time the vessels incorporated into the septum (Fig. 14) produce a porto-hepatic venous shunt as described in human[9] and experimental cirrhosis.[28] Owing to these shunts which may be considered as internal Eck fistulas, blood by-passes the parenchyma, which is placed under unfavorable circulatory conditions. The resulting hepatocellular injury may aggravate the pre-existing inflammatory reaction in the portal triads; new membranes forming around the primary septa develop into secondary septa which in turn lead to further subdivision of the primary nodules (Text-fig. 3). These secondary nodules grow at variable speeds and an irregular picture develops. With the processes characteristic of nodule formation, the lobular architecture is abolished and the original central vein is excluded from the parenchyma.

Mechanics of Septum Formation. If the central and portal veins ran parallel to each other, as depicted in the well known stereogram of the liver lobule in Braus' book,[29] the primary nodules would be long columns; however, portal and hepatic venous branches cross at approximately right angles in space.[7,22,23] This makes it necessary for the septa connecting the hepatic and portal canals to be twisted (Text-fig. 4A), and this, in turn, influences their shape. The septa cannot isolate the nodules completely from one another; however, each septum has two free edges. These edges are often indistinct, but far more frequently they are sharply outlined. Upon reconstruction (Text-fig. 4B), when the free edges are sharp, they have the shape of a concave line. Such a shape will be developed if a line firmly attached at both ends (slender arrows, Text-fig. 4B) is exposed to a transverse resistance (stout arrows, Text-fig. 4B). The points of attachment of primary septa are at the portal and hepatic canals. The points of attachment of secondary septa are at the primary septa. The resistance is offered by the parenchyma which prevents the straightening of the line. As a rule, the septa are flat, reflecting the tension to which they are exposed. This tension is due to expansion of the parenchyma which pushes the points of insertion of the septa apart, or it is due to



Text-fig. 4. A. Stereogram. The interdigitation of the portal and hepatic venous tree causes: (a) torsion of the septa connecting portal and central canals and (b) free edges of the septa, preventing complete separation of the nodules from each other. (Text-fig. 4A is reproduced by permission of the Josiah Macy, Jr. Foundation from *Transactions of the 11th Conference on Liver Injury,* 1952, page 191.) B. Reconstruction of septum with free edge distorting efferent venule which becomes tortuous. Slender arrows indicate traction; stout arrows, tissue resistance. C. Crooked septum indicative of lack of tension and efferent vessels. Mallory's aniline blue stain. × 80. D and E. Reconstruction of small regenerating nodule: D, surface appearance; E, cut surface. All cells are in contact with sinusoids. In D, connection with a ductule is shown.

contraction of the membranes forming the septa; or it may be due to both. The often noted wavy character of such membranes (Fig. 12) may be evidence of contraction.

Processes Inherent in Nodule Formation. When part of a lobule becomes separated from the rest of the parenchyma, several characteristic changes develop.

1. The liver plates are rearranged owing to alteration of the sinusoidal blood flow. The concentric direction toward the central vein of the lobule is abandoned, and after some irregular arrangement, a new concentric arrangement is resumed toward the center of the nodule (Fig. 16, lower right; Fig. 17).

2. New efferent venules develop from intranodular sinusoids; these efferent venules are tortuous, primarily because of their origin from sinusoids, and secondarily, because of distortion by the advancing septa (Text-figs. 4B and 4C).

3. The parenchyma undergoes regeneration, partly owing to the proximity to liver cell destruction and partly owing to humoral effects in the presence of destruction of hepatic parenchyma anywhere in the liver.[30] This regeneration produces plates two or more cells thick (Fig. 17) throughout the smaller nodules. In larger nodules such plates are seen near the periphery of the lobules; in the center, the plates are one cell in thickness (Fig. 18). Rapidly regenerating nodules compress the surrounding connective tissue which thus passively may assume the shape of a septum; or the membranes may be disrupted and transformed into palisades of parallel fibers. The veins around such nodules are compressed. The tributaries of the hepatic veins are flattened since they have only a thin connective tissue cover.

4. Isolated cells or cell groups may become trapped in the connective tissue. Some of them are fat-containing and may even develop into fatty cysts.[31] These isolated cells or cell groups may become atrophic; they may die, or they may start regenerating, forming a group of cells not separated by sinusoids (Fig. 21). Eventually, a well vascularized small nodule may form from such trapped cells. The nodule will contain at its periphery plates of several cell thicknesses (Text-fig. 4D). At a later stage (Fig. 19) the plates will become thinner toward the center; in the larger nodules, they become one cell in thickness. Circulatory disturbances may lead to atrophic thinning and even necrosis of cells in the center of the nodule (Fig. 20).

5. On the border of the lobules the liver cell plates may be transformed into bile ducts of the smallest size or cholangioles (Fig. 22). In accordance with the embryologic observation[32] that cholangioles originate from liver cells rather than vice versa, the connection of these proliferating cells with the biliary duct system has often been observed[33] and demonstrated by reconstruction (Text-fig. 4D).

Comment. The development of cirrhosis as a result of periportal inflammation starts with a radiating periportal collagenous membrane formation (membranosis), a process commonly seen under the most diverse circumstances. The histogenesis of this membranosis requires further elucidation. In view of the absence of fibroblasts, it is still possible to defend the old theory[10,34] that plasma protein which has escaped into the tissue spaces (serous hepatitis) is the stimulus and furnishes the material for the collagenous membranes. Recently such a process occurring in children in Jamaica as the result of either malnutrition and/or toxicity was called collagenosis[35]; however, inasmuch as collagen differs chemically from plasma proteins, additional histochemical studies concerning membrane formation in the liver and regarding the influence of liver cell breakdown products on membrane formation are required.

This radiating periportal membranosis usually remains stationary. Sometimes, for reasons not obvious, membranes may aggregate and the intervening liver cells disappear, so that thicker septa form, extending into the lobular parenchyma. The sheet-like septa may connect portal triads with each other (perilobular "fibrosis"), but may extend into the lobular parenchyma itself and connect portal with hepatic fields.

Inasmuch as the portal and hepatic venous trees interdigitate in space, they cut out portions of the lobule; eventually secondary septa increase the subdivision. Nodules of various sizes and shapes are formed. Rearrangement of the liver cell plates, formation of new efferent venules, and irregular regeneration contribute to the abolition of the lobular architecture. This is aggravated by a counteraction between the nodules expanding as a result of regeneration and the tension and contraction of the connective tissue of the septa. It should be emphasized that in the cirrhotic liver, expansion of the regenerating parenchyma may exceed the resistance offered by the usually tough collagenous connective tissue (Text-fig. 4C).

Central Toxic Necrosis

After central necrosis and collapse of the framework in the central zone, membranes may develop which radiate from the central vein. Some membranes become aggregated to produce septa that connect hepatic canals with each other, but eventually also hepatic with portal canals. These septa thus subdivide the lobule. Central toxic hepatic necrosis usually is associated with periportal inflammation and subsequent radiating membranosis. Septa originating from the portal triads interconnect with those from the central fields to produce a similar dissection of the lobule with nodule formation occurring in the manner described.

Comment. Single toxic insults are usually not followed by septum formation. Repeated attacks are required[6] as seen, for instance, in carbon tetrachloride[36] or bromobenzene[37] intoxication.

Passive Congestion

Membrane and septum formation following centrolobular necrosis in acute passive congestion do not differ from those following toxic central necrosis.[38] Initially, owing to a reduction of the normal portohepatic blood pressure gradient,[39] the liver cell plates and the sinusoids rearrange themselves to radiate from the portal canals. Then the areas of necrosis connect neighboring central veins in a bridge-like fashion, so that the periportal regions appear surrounded by continuous red, congested areas and the lobular pattern seems inverted. In longer standing congestion, radiating membranosis develops around the central vein, sometimes extending into the bridges of necrosis which connect the central veins.[40] This does not yet constitute cirrhosis, however. Eventually in rare instances, a cardiac cirrhosis develops. In such cases the lobular architecture is distorted when septa have come to connect central and portal fields. This may be facilitated if periportal inflammation complicates the congestion.

Comment. The processes of development of the rare cardiac cirrhosis[41] are similar to those following central toxic necrosis.

Fatty Metamorphosis

Connective tissue accumulation in the fatty liver preceding and possibly leading to the formation of cirrhosis may occur as a result of several processes:

1. In livers with advanced fatty metamorphosis, fissures are frequently noted (Fig. 23). The constancy of their appearance and their direction, which is not related to that of the microtome knife, speaks against their being artifacts. They range from 10 to 25 μ in width, often radiate from a portal triad, and may traverse long distances. As straight lines in sections, they represent flat fissures in three-dimensional space. When two hepatic regions break apart owing to uneven expansion, the border of these regions produces a fissure. The following processes may be responsible for uneven expansion:

(a) Foci of necrosis occur frequently in the fatty liver and, as a result of contraction, they may be separated by fissures from the intact or even regenerating tissue.

(b) Regeneration with development of fat-free plates two-cells thick may occur in some hepatic territories following recovery from fatty degeneration (Fig. 24). This may take place particularly in the periportal areas which are in general more likely to regenerate. Also formation of intensely regenerating nodules induces fissures in their vicinity, in these instances as a result of expansion.

(c) In chronic fatty metamorphosis some areas temporarily recover, especially in the common nutritional forms when periods of poor nutrition may alternate with those of better nutrition. More fat and larger droplets are sometimes noted on one side of the fissure than on the other (Figs. 23 and 27). This reflects different rates of fat deposition resulting in different rates of expansion.

Within the fissures liver cells disappear and collagenous membranes or fibers develop which aggregate to form septa (Fig. 25). In the sections the completed septa appear as straight lines without tension (Fig. 26), which originate in most instances in the portal triads.

In prolonged fatty metamorphosis, the fat droplets of several liver cells coalesce to form fatty cysts as demonstrated by Hartroft and Ridout[31] in choline-deficient rats (Fig. 28). As they described it, after disappearance of the fat the shells of the fatty cysts collapse and give rise to connective tissue membranes. In addition, collagenous membranes (Fig. 29) or fibers (Fig. 30) develop in the vicinity of the fatty cysts but independent of them in regenerating masses of liver cells, forming plates from two to several cells thick.

2. Around the frequent areas of periportal inflammation in fatty cirrhosis, membranes form following the pattern described under *periportal inflammation.* These membranes eventually result in dissection of the lobule (Fig. 31). Membrane formation around intralobular foci of necrosis may also contribute (Fig. 32).

The morphogenesis of the septa in fatty cirrhosis is not easily recognized in the advanced stage but becomes apparent in the transition of fatty liver into fatty cirrhosis.[42] Septa resulting from inflammation and developing septa in fissures are of greater importance than those developing around fatty cysts. The septa of different origin, however, have the same effect in distorting the lobular architecture. Reconstruction shows that they do not separate the nodules completely from one another (Fig. 33).

Comment. Multiple pathways have been described to explain the development of cirrhosis from fatty liver. Some investigators[6,43,44] have assumed that the deposition of fat itself causes the fibrosis, whereas others have expressed doubt as to whether fatty metamorphosis, as such, induces cirrhosis,[45-47] and have pointed out that in man, fatty metamorphosis may persist for a long time without producing anything more than portal "stellate" fibrosis. In the malignant malnutrition of kwashiorkor, for instance, cirrhosis develops after a long interval in which the liver is fat-free.[45] Similarly, in ethionine intoxication of the rat, fatty liver develops but disappears again, and fibrotic and cirrhotic transformation follows after a prolonged fat-free period.[48]

Of the pathways illustrated here by three-dimensional reconstruction, only one is related to the fat deposition directly; namely, the membrane formation following the collapse of fatty cysts as described by Hartroft.[31,43] This appears to be the most important process in choline-deficient rats. In man, however, this seems to be in the background compared to two other processes which are only indirectly related to fat deposition. One is represented by the septa which develop from inflammatory changes in and around the portal triads and in the parenchyma, often associated with necrosis and regeneration. These inflammatory and necrotizing changes occur more commonly in the fatty liver than in the normal liver, and are a reflection that the fatty liver is more sensitive to infections or other injuries.[42] The other is the development of fissures due to stress resulting from uneven tissue turgor caused by variation in fat deposition, necrosis, and intralobular periportal and nodular regeneration. This is followed by formation of membranes and straight septa. Variations in the structure of the liver in time and space, therefore, appear more important than the permanency of the fat deposition and explain why fatty metamorphosis does not necessarily lead to cirrhosis in man.

In agreement with clinical observations, it appears that episodes of necrosis associated with infections or other injuries anywhere in the body, as well as subsequent regeneration and variation in the degree of nutritional disturbance, again associated with subsequent regeneration, are of greater importance in man in the transition into cirrhosis than is the fat deposition itself.[42]

Pericholangiolitis

Chronic inflammatory changes in and around the cholangioles are associated with connective tissue proliferation. The connecting pieces between the bile capillaries and the interlobular bile ducts in the portal triads have been designated as septal ducts[49,50] or canals of Hering, or cholangioles or ductules.[30] Ductules are found in greatest number in the normal liver around the portal triads, but they also pervade the hepatic parenchyma as first described by Eberth[51] and subsequently by Clara.[52] They do not end blindly but form loops anastomosing with other intralobular ductules deep in the lobular parenchyma.[7] For a considerable distance, they are accompanied by intralobular arterioles or arterial capillaries and, occasionally, by an extremely thin lymph vessel which can be demonstrated by India ink injection.[7] These intralobular conduits are surrounded by a common delicate sheet of connective tissue which constitutes their common adventitia and which itself is arranged in filamentous form. Normally, the intralobular ductules are small, less than 4 μ in diameter, and can be seen only at high magnification. Sometimes, however, they become enlarged up to 20 μ in diameter (Fig. 34) and are easily visible. The causes of this transformation, sometimes associated with jaundice, are as yet unknown.

Inflammatory cellular exudate may accumulate around the periportal and intralobular ductules. Around the latter, it is found within the described adventitial sheets, and it therefore cannot be decided whether the lesion represents a pericholangiolitic or a perilymphangitic infiltration. In prolonged cases of extrahepatic as well as of intrahepatic cholestasis (cholangiolitis),[53-56] these changes are especially apparent, and eventually sometimes rather coarse connective tissue fibers appear in the pre-existing connective tissue trabeculae which thus become more conspicuous (Figs. 35 and 36). In reconstruction, the trabeculae appear curved and cylindriform (Fig. 38). Even if these trabeculae are numerous and liver cell groups appear separated from one another by them (Fig. 37), the lobular pattern is not destroyed. Eventually, however, membranes appear first around the portal triads (perilobular fibrosis) and subsequently connect the portal triads with the trabeculae and dissect the lobules as they extend into them (Fig. 39).

Comment. The pericholangiolitic type of fibrosis, even if conspicuous, differs from the previously described cirrhosis in that cylindriform trabeculae rather than flat septa develop, at least in the pure form. These trabeculae traverse the lobular parenchyma, initially representing a reinforcement of the common adventitia of the intralobular arterioles, ductules, and lymphatics. With further proliferation of the ductules, this cylindriform system may become rather dense; nevertheless, the lobules are not dissected. In view of the intact lobular pattern, this lesion does not represent cirrhosis in the sense of the definition given and could be called pericholangiolitic pseudo-cirrhosis. It is not, as a rule, associated with portal hypertension nor with ascites. Many of these pure lesions are associated with severe jaundice and resemble primary biliary cirrhosis or Hanot's[5] or cholangiotoxic cirrhosis.[10] Only in later stages of this lesion do septa form, possibly owing to a complicating bacterial infection of the portal triads or other causes of necrosis. This is associated with dissection of the lobules and produces, in turn, portal hypertension as is usually seen in later stages of "cholangiolitic" cirrhosis.[54-56]

Discussion

The development of each type of cirrhosis is an extremely complicated four-dimensional process in which the three dimensions of space and the fourth dimension of time must be considered. The material for this study, however, consists essentially of two-dimensional serial sections of fixed tissue, the dimension of time having been eliminated by the death of the patient, the dimension of depth having been lost in the microtome. From these two-dimensional shadows and by the application of analytic mechanical principles, the attempt was made to reconstruct the four-dimensional process.

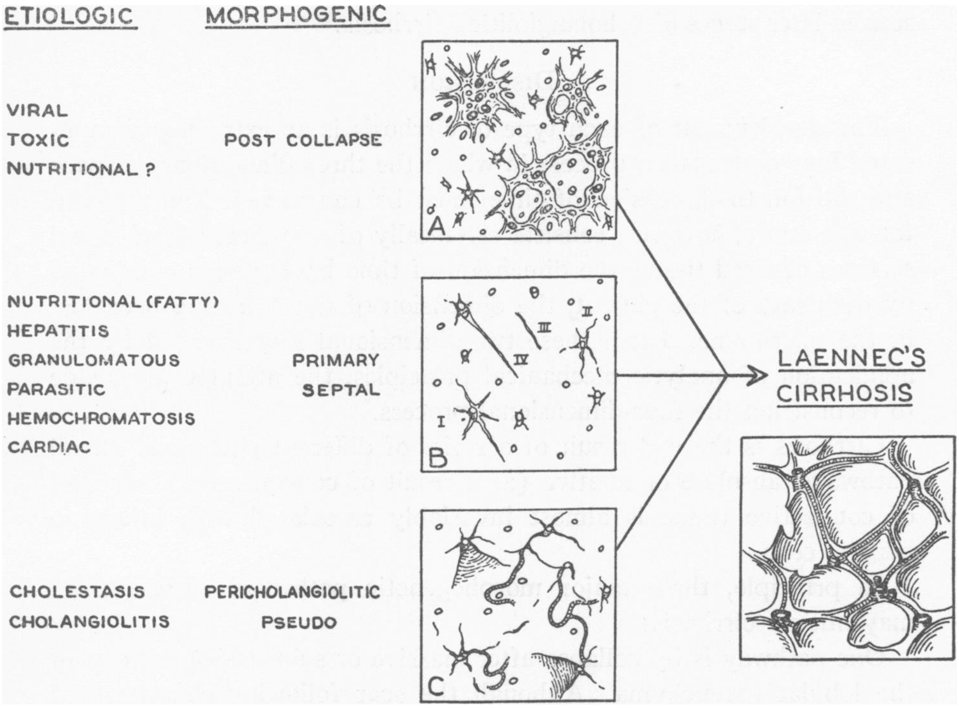
Cirrhosis is the end result of a series of different pathways. In all pathways, absolute or relative (as a result of condensation), increase of connective tissue is almost invariably associated with injury to hepatic cells.

In principle, three major morphogenetic pathways (Text-fig. 5) may initiate cirrhosis:

One pathway is by collapse after massive or submassive necrosis of the lobular parenchyma. Although the scar following collapse does not represent cirrhosis, septa resulting from fissures and periportal inflammation, as well as the formation of nodules of variable sizes and shapes in the surrounding tissue cause cirrhotic transformation, for which the term post-collapse cirrhosis may be justified. Typically, the lesion is not uniform in different parts of the liver and many portal triads and central canals may be entirely uninvolved either in larger nodules or in the lobular parenchyma. Although viral infections are probably the most important cause, intoxications cannot be excluded and, at least in the Tropics, malnutrition may be causative.

The second pathway is by the primary formation of septa: (1) from the portal triad; (2) from the central canal; (3) within the lobular parenchyma; or, (4) within fissures owing to uneven expansion of hepatic territories. Focal necrosis, fatty metamorphosis, and irregular regeneration are among the stimuli for this septum formation, which has a tendency to be uniform throughout and to involve all lobules.

Since primary septum formation in these instances causes the subdivision of the lobule and the formation of regenerative nodules, the term primary septal cirrhosis could be proposed for a lesion which may have several causes. Most important is probably malnutrition (which causes fatty metamorphosis). However, primary septal cir-



Text-fig. 5. Schematic presentation of etiologic and morphogenetic factors, as well as of the pathways for the development of cirrhosis.

rhosis may also be due to hepatitis of various causes, granulomatous diseases, hemochromatosis, parasitic infestation, and even passive congestion.

The third pathway starts with the accumulation of fibrous connective tissue around perilobular and intralobular ductules (pericholangiolitis) to produce a cylindriform network traversing the lobule but not dissecting it; therefore, the term cirrhosis does not apply to this stage, for which the term pericholangiolitic pseudo-cirrhosis could be used. In later stages, however, septum formation ensues with subdivision of the lobule, and it then becomes difficult to recognize the morphogenesis of the lesion which may be due to intrahepatic changes associated with cholestasis or, though rarely, to extrahepatic mechanical biliary obstruction.

It appears that eventually septum formation takes place in all three forms and a common terminal pathway results, for which the term Laennec's cirrhosis is proposed in analogy to the term Bright's disease applied to a similar stage in renal diseases.[30] The initial pathway may sometimes be recognized by large scars and large nodules in cases following massive necrosis and collapse[1,5]; but there are many cases of similar etiology in which small nodules of a diffuse septal cirrhosis are in the foreground.[19,21]

It should be stressed that the terms proposed refer to morphogenetic pathways and not to etiologic entities. The same liver may show indications of two pathways; for instance, in the diffuse septal cirrhosis due to alcoholic or tropical malnutrition, large scars resulting from primary and secondary collapse may be complicating features. The terms, therefore, are only partly comparable to the designations in general use. With this reservation, *post-collapse cirrhosis* corresponds to what is often called toxic,[1] or post-necrotic cirrhosis,[5] chronic liver atrophy,[20] or coarse nodular hyperplasia. *Primary septal cirrhosis* refers to lesions sometimes designated as portal or Laennec's cirrhosis, whereas *pericholangiolitic pseudocirrhosis* corresponds to some forms of biliary or Hanot's cirrhosis.[5,56]

For the basic clinical manifestations of cirrhosis, two morphologic features, common to all types, can be made to account; namely, the regenerative nodule and the anastomoses between portal and hepatic veins. In the regenerative nodule the liver cell plates have rearranged themselves. The direction of the liver cell plates in general reflects the direction of the blood flow,[49,39] and the altered flow in the nodule results in a tendency of the plates to become arranged concentrically to the new center of the nodule and independent of the center of the original lobule. Regeneration within the nodule is the result of an attempt to replace liver tissue near the interruption of the plate on the border of the nodules; but it is also the result of humoral effects caused by the reduction of liver tissue in general. This distant effect can be compared to the regeneration occurring in the intact liver of one of a pair of parabiotic rats when a partial hepatectomy has been performed on the other rat.[57] This regeneration leads to compression of the hepatic veins[9,11] which represents an important cause of portal hypertension in cirrhosis,[11] probably mechanically more important than excess of arterial blood supply to the cirrhotic septa.[22] The smaller the regenerative nodules, the more effective is their compression of the hepatic veins; therefore, the degree of portal hypertension is greater in the fine nodular form than in the coarse nodular form.[21]

The porto-hepatic venous anastomoses develop either in collapsed areas where sinuses persist or in the septa that connect the portal with the central field. In the septa the vessels usually form a dense network in which hepatic arterial branches participate,[22] as seen in injection preparations.[9,22] Through the anastomoses, blood is shunted from the portal to the hepatic vein, by-passing the lobular or nodular parenchyma and putting the parenchyma at a circulatory disadvantage. These shunts do not relieve portal hypertension because the compression of the hepatic veins previously described occurs closer to the heart than do these anastomoses. The anastomoses are considered responsible for nutritional disturbances and anoxia of the lobular parenchyma in cirrhosis; anastomoses likewise account for some of the instances of hypoxic (secondary) necrosis seen frequently in the center of the lobules and nodules. The shunts maintain injury to the cirrhotic parenchyma which persists even when the original or predisposing cause of cirrhosis, such as fatty metamorphosis or virus infection, has long disappeared. The central necrosis of lobules and nodules may become extensive and even submassive. Some cells of such a necrotic nodule or lobule may survive and become trapped in the connective tissue, either as isolated cells or in groups. They may eventually grow into new nodules. These nodules may become necrotic again in a never-ending cycle, characteristic of cirrhosis.

Summary

The attempt has been made to demonstrate the pathways of the architectural changes of the liver in various types of cirrhosis and to explain the mechanical processes associated with them.

1. One pathway results from the sequelae of massive and submassive necrosis of the lobular parenchyma with subsequent collapse, leading to post-collapse cirrhosis. The vessels and ducts are approximated and the angles of branching become acute without disturbance of the basic arrangement of interdigitation of the portal and hepatic canals. In the surrounding liver tissue a pattern of traction is created by the collapse of the necrotic area, and fissures arise in which connective tissue septa develop. Lobular fragments in submassive necrosis become nodules which either represent part of a lobule or may be composed of multiple lobules.

2. The second pathway leads to primary septal cirrhosis through the formation of septa by aggregation of collagenous membranes. The septa have formed either in the lobular parenchyma as reinforcement of the argentaffin fiber network or in stress fissures separating hepatic

territories of uneven expansion caused by regeneration, necrosis, and irregular fatty metamorphosis. Septa may originate from either portal or central canals or develop within the parenchyma. They may cut out nodules of various sizes from the lobule, especially if they connect central and portal canals. In the nodules, rearrangement of the liver cell plates, formation of a new efferent vein, and intense regeneration develop. The intense regeneration is reflected in plates several cells thick and in the formation of ductules.

In fatty metamorphosis septation may be the result of several processes: (a) collapse of fatty cysts; (b) periportal and intralobular necrosis and inflammation; and (c) membrane formation in stress fissures caused by uneven expansion of hepatic territories from irregular fat deposition, regeneration, and necrosis. Since processes (b) and (c) predominate in the human liver, cirrhosis from fatty metamorphosis does not result from fat deposition directly, but from increased susceptibility of the fatty liver to necrotizing or inflammatory processes and subsequent regeneration.

3. In pericholangiolitis, fibrous connective tissue proliferation in the adventitia of intralobular ductules creates irregularly curved cylindriform trabeculae. Even if this connective tissue formation becomes extensive (pericholangiolitic pseudo-cirrhosis), the lobule is not subdivided until late when septa form because of accompanying processes, and cirrhosis develops.

4. All three pathways—collapse, septation, and formation of cylindriform trabeculae—may terminate in a common pathway with extensive development of septa and nodules, for which the term Laennec's cirrhosis is proposed.

5. One feature common to any cirrhosis is nodule formation (a) from lobular fragments after collapse, (b) from subdivisions of the lobule by septa, or (c) from regeneration of trapped cells within the septa. The regenerating nodules compress the hepatic veins, thus accounting for portal hypertension. A second feature is porto-hepatic venous anastomoses by inclusion of sinusoids in developing septa. These shunt blood past the parenchyma and thus produce unfavorable circulatory conditions for it. Central necrosis ensues, setting in motion a cycle of degeneration and regeneration, characteristic of cirrhosis and independent of the persistence of its original cause.

REFERENCES

1. Mallory, F. B. Cirrhosis of the liver. *New England J. Med.*, 1932, 206, 1231–1239.
2. Moon, V. H. Histogenesis of atrophic cirrhosis. *Arch. Path.*, 1932, 13, 691–706.

3. Eppinger, H. Die Leberkrankheiten. Allgemeine und spezielle Pathologie und Therapie der Leber. Julius Springer, Vienna, 1937, 801 pp.
4. Hart, J. F., and Lisa, J. R. Histogenesis of Laennec's cirrhosis. *New York State J. Med.*, 1937, **37**, 1619–1626.
5. Karsner, H. T. Morphology and pathogenesis of hepatic cirrhosis. *Am. J. Clin. Path.*, 1943, **13**, 569–606.
6. Himsworth, H. P. Lectures on the Liver and Its Diseases: Comprising the Lowell Lectures Delivered at Boston, Massachusetts, in March, 1947. Harvard University Press, Cambridge, 1947, 204 pp.
7. Elias, H. A re-examination of the structure of the mammalian liver. II. The hepatic lobule and its relation to the vascular and biliary systems. *Am. J. Anat.*, 1949, **85**, 379–456.
8. Elias, H., and Spanier, E. H. Structure of the collagenous tissue in the cirrhotic liver, a contribution to the geometry of sectioning. *Ztschr. f. wissensch. Mikr.*, 1953, **61**, 213–221.
9. Popper, H.; Elias, H., and Petty, D. E. Vascular pattern of the cirrhotic liver. *Am. J. Clin. Path.*, 1952, **22**, 717–729.
10. Rössle, R. Entzündungen der Leber. In: Henke, F., and Lubarsch, O. Handbuch der speziellen pathologischen Anatomie und Histologie. Julius Springer, Berlin, 1930, **5**, 243–505.
11. Kelty, R. H.; Baggenstoss, A. H., and Butt, H. R. The relation of the regenerated liver nodule to the vascular bed in cirrhosis. *Gastroenterology*, 1950, **15**, 285–295.
12. Elias, H. The liver cord concept after one hundred years. *Science*, 1949, **110**, 470–472.
13. Randall, J. T.; Fraser, R. D. B.; Jackson, S.; Martin, A. V. W., and North, A. C. T. Aspects of collagen structure. *Nature, London*, 1952, **169**, 1029–1033.
14. Glegg, R. E.; Eidinger, D., and Leblond, C. P. Some carbohydrate components of reticular fibers. *Science*, 1953, **118**, 614–616.
15. Elias, H., and Popper, H. Histochemical factors in the formation of hepatic cirrhosis. (In preparation.)
16. Lucké, B., and Mallory, T. The fulminant form of epidemic hepatitis. *Am. J. Path.*, 1946, **22**, 867–945.
17. Popper, H., and Franklin, M. Viral versus toxic hepatic necrosis. *Arch. Path.*, 1948, **46**, 338–376.
18. Elias, H., and Pauly, J. E. Strukturelemente in menschlichen Nebennierenrinden. *Anat. Anz.*, 1953, **100**, 134–147.
19. Werthemann, A., and Bodoky, G. Die pathologische Anatomie der gehäuften Leberdystrophiefälle von Basel aus dem Jahre 1946. *Schweiz. Ztschr. f. Path. u. Bakt.*, 1947, suppl., **10**, 176–201.
20. Bjørneboe, M., and Raaschou, F. The pathology of subchronic atrophy of the liver. *Acta med. Scandinav.*, 1949, suppl. **234**, 41–62.
21. Baggenstoss, A. H., and Stauffer, M. H. Post-hepatitic and alcoholic cirrhosis: clinicopathologic study of 43 cases of each. *Gastroenterology*, 1952, **22**, 157–180.
22. McIndoe, A. H. Vascular lesions of portal cirrhosis. *Arch. Path.*, 1928, **5**, 23–42.
23. Elias, H., and Petty, D. Gross anatomy of the blood vessels and ducts within the human liver. *Am. J. Anat.*, 1952, **90**, 59–111.

24. Elias, H.; Bond, E., and Lazarowitz, A. The "normal" liver of the pig; is it an example of purely portal (and therefore subclinical) cirrhosis? A preliminary report. *Am. J. Vet. Research,* 1954, **15,** 60–66.

25. Thaler, H. Über die formale Pathogenese der posthepatitischen Lebercirrhose. *Beitr. z. path. Anat. u. z. allg. Path.,* 1952, **112,** 173–186.

26. Benz, E. J.; Baggenstoss, A. H., and Wollaeger, E. E. Atrophy of the left lobe of the liver. *A. M. A. Arch. Path.,* 1952, **53,** 315–330.

27. Moschcowitz, E. Laennec cirrhosis. Its histogenesis, with special reference to the role of angiogenesis. *Arch. Path.,* 1948, **45,** 187–215.

28. Ungar, H. Transformation of the hepatic vasculature of rats following protracted experimental poisoning with carbon tetrachloride. Its possible relation to the formation of urate calculi in the urinary tract. *Am. J. Path.,* 1951, **27,** 871–883.

29. Braus, H. Anatomie des Menschen. Julius Springer, Berlin, 1924, **4,** p. 317.

30. Popper, H. Liver disease—morphologic considerations. *Am. J. Med.,* 1954, **16,** 98–117.

31. Hartroft, W. S., and Ridout, J. H. Pathogenesis of the cirrhosis produced by choline deficiency. Escape of lipid from fatty hepatic cysts into the biliary and vascular systems. *Am. J. Path.,* 1951, **27,** 951–989.

32. Horstmann, E. Entwicklung und Entwicklungsbedingungen des intrahepatischen Gallengangsystems. *Arch. f. Entwcklngsmechn. d. Organ.,* 1939, **139,** 363–392.

33. Hess, O. Über die bei der akuten gelben Leberatrophie auftretenden Regenerationsprozesse. *Beitr. z. path. Anat. u. z. allg. Path.,* 1913, **56,** 22–62.

34. Eppinger, H.; Kaunitz, H., and Popper, H. Die seröse Entzündung. Julius Springer, Vienna, 1935, 298 pp.

35. Hill, K. R.; Rhoades, K.; Stafford, J. L., and Aub, R. Liver disease in Jamaican children (serous hepatosis). *West Indies M. J.,* 1951, **1,** 49–63.

36. Cameron, G. R., and Karunaratne, W. A. E. Carbon tetrachloride cirrhosis in relation to liver regeneration. *J. Path. & Bact.,* 1926, **42,** 1–21.

37. Popper, H. Unpublished observations.

38. Wallach, H. F., and Popper, H. Central necrosis of the liver. *Arch. Path.,* 1950, **49,** 33–42.

39. Elias, H., and Sokol, A. Dependence of the lobular architecture of the liver on the porto-hepatic blood pressure gradient. *Anat. Rec.,* 1953, **115,** 71–85.

40. Sherlock, S. The liver in heart failure; relation of anatomical, functional and circulatory changes. *Brit. Heart J.,* 1951, **13,** 273–293.

41. Moschcowitz, E. The morphology and pathogenesis of cardiac fibrosis of the liver. *Ann. Int. Med.,* 1952, **36,** 933–955.

42. Popper, H.; Szanto, P. B., and Elias, H. Transition of fatty liver into cirrhosis. *Gastroenterology,* 1955, **28,** 183–192.

43. Hartroft, W. S. Accumulation of fat in liver cells and in lipodiastaemata preceding experimental dietary cirrhosis. *Anat. Rec.,* 1950, **106,** 61–87.

44. Connor, C. L. Fatty infiltration of the liver and the development of cirrhosis in diabetes and chronic alcoholism. *Am. J. Path.,* 1938, **14,** 347–364.

45. Davies, J. N. P. Nutrition and Nutritional Diseases. In: Cutting, W. C. (ed.) Annual Review of Medicine. Annual Reviews, Inc., Stanford, Calif., 1952, **3,** 99–132.

46. Dible, J. H. Degeneration, necrosis, and fibrosis in the liver. *Brit. M. J.*, 1951, **1**, 833–841.

47. György, P. Experimental hepatic injury. *Am. J. Digest. Dis.*, 1952, **19**, 392–396.

48. Popper, H.; De la Huerga, J., and Koch-Weser, D. Hepatic injury due to conditioned sulfo amino acid deficiency. *Ann. New York Acad. Sc.*, 1954, **57**, 936–947.

49. Pfuhl, W. Die Leber. In: von Möllendorff, W. Handbuch der mikroskopischen Anatomie des Menschen. Julius Springer, Berlin, 1932, **2**, 235–425.

50. MacMahon, H. E., and Thannhauser, S. J. Congenital dysplasia of the interlobular bile ducts with extensive skin xanthomata: congenital acholangic biliary cirrhosis. *Gastroenterology*, 1952, **21**, 488–506.

51. Eberth, C. J. Untersuchungen über die normale und pathologische Leber. *Virchows Arch. f. path. Anat.*, 1867, **39**, 70–89.

52. Clara, M. Untersuchungen an der menschlichen Leber. I. Teil. Über den Übergang der Gallenkapillaren in die Gallengänge. *Ztschr. f. mikr.-anat. Forsch.*, 1930, **20**, 584–607.

53. Hanger, F. M., Jr., and Gutman, A. B. Postarsphenamine jaundice apparently due to obstruction of intrahepatic biliary tract. *J. A. M. A.*, 1940, **115**, 263–271.

54. Watson, C. J., and Hoffbauer, F. W. The problem of prolonged hepatitis with particular reference to the cholangiolitic type and to the development of cholangiolitic cirrhosis of the liver. *Ann. Int. Med.*, 1946, **25**, 195–227.

55. MacMahon, H. E., and Thannhauser, S. J. Xanthomatous biliary cirrhosis (a clinical syndrome). *Ann. Int. Med.*, 1949, **30**, 121–179.

56. Ahrens, E. H., Jr.; Payne, M. A.; Kunkel, H. G.; Eisenmenger, W. J., and Blondheim, S. H. Primary biliary cirrhosis. *Medicine*, 1950, **29**, 299–364.

57. Bucher, N. L. R.; Scott, J. F., and Aub, J. C. Regeneration of the liver in parabiotic rats. *Cancer Research*, 1951, **11**, 457–465.

LEGENDS FOR FIGURES

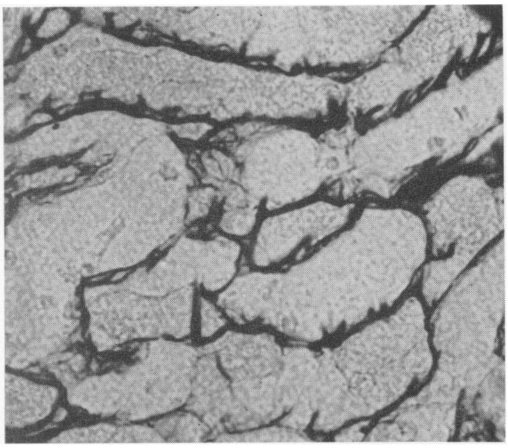
FIG. 1. Intact network of reticulum fibers during acute massive necrosis. Gomori's silver impregnation. × 450.

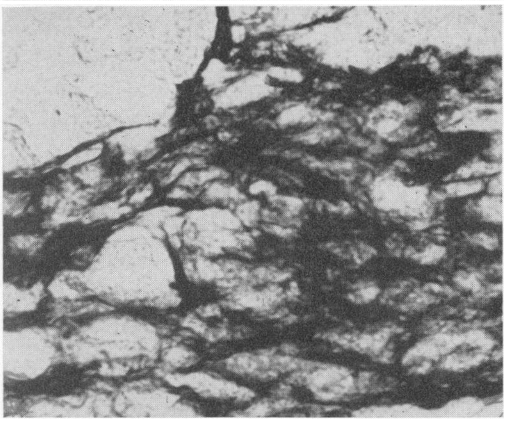
FIG. 2. Collapsed network of reticulum fibers after massive necrosis. Gomori's silver impregnation. × 450.

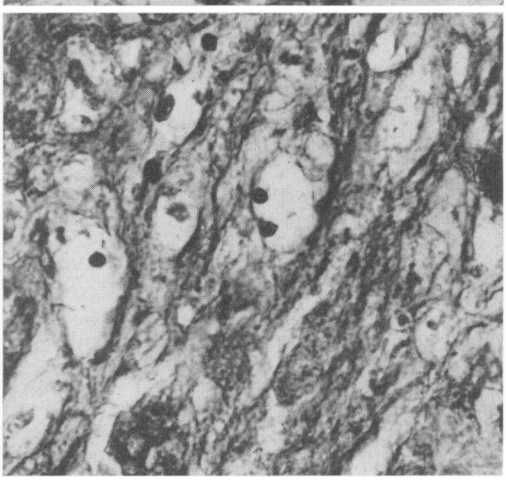
FIG. 3. Fuchsinophilic fibrillar material in area undergoing collapse. Section stained with van Gieson's stain and photographed on high contrast film. × 450.

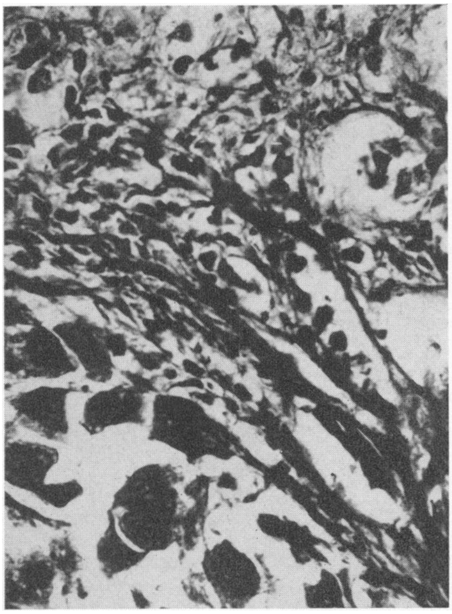
FIG. 4. Delicate collagenous membranes in collapsed area. Van Gieson's stain. × 450.

FIG. 5. Network of reticulum fibers in the same collapsed area as shown in Figure 4. Gomori's silver impregnation. × 450.


1


2


3


4

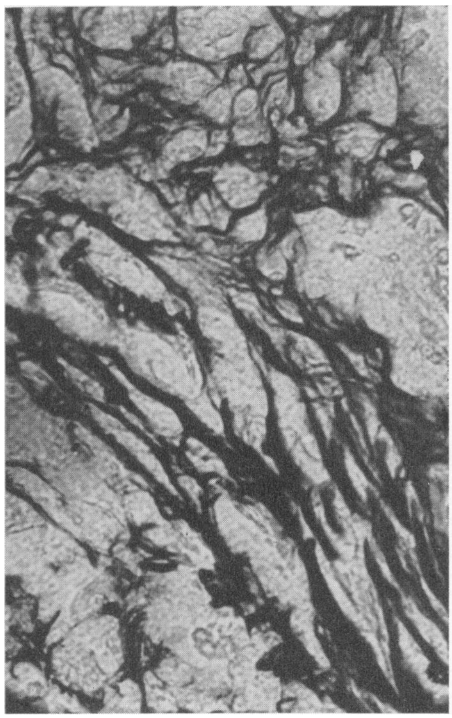
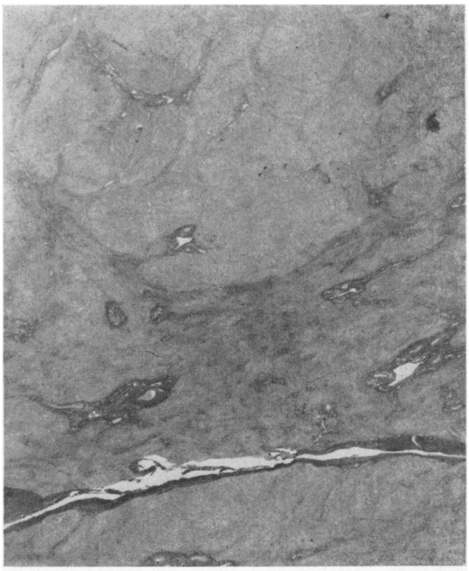

5

FIG. 6. Large scar resulting from collapse after massive necrosis (viral hepatitis). Approximation of portal and hepatic fields. Van Gieson's stain. × 61.

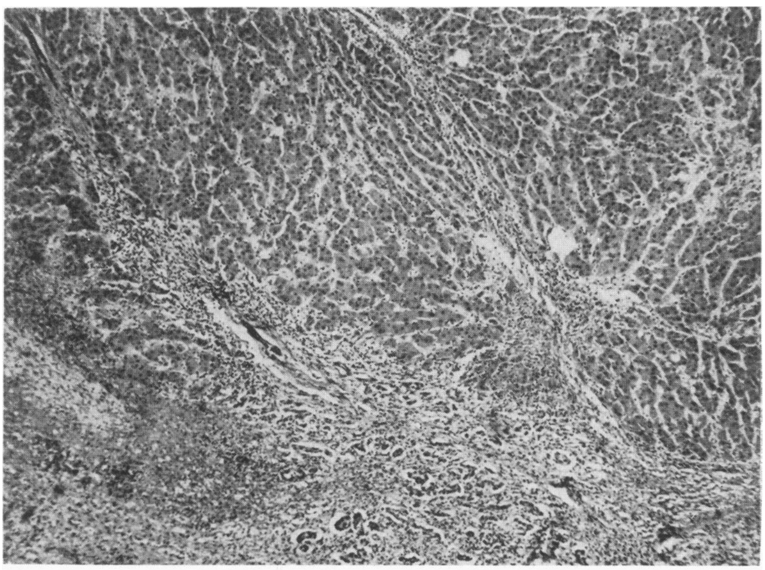
FIG. 7. Area of collapse after massive necrosis. Sharp difference between coarse fibers in portal and central canals, and delicate membranes in collapsed parenchyma. Van Gieson's stain. × 150.

FIG. 8. Parenchyma bordering on massive necrotic area showing fissure due to traction resulting from adjacent collapse. These fissures have no relation to the lobular topography. Hematoxylin and eosin stain. × 60.



6

7



8

FIG. 9. Submassive collapse in viral hepatitis, with lobular fragments becoming nodular, and fissure due to stress. Hematoxylin and eosin stain. × 60.

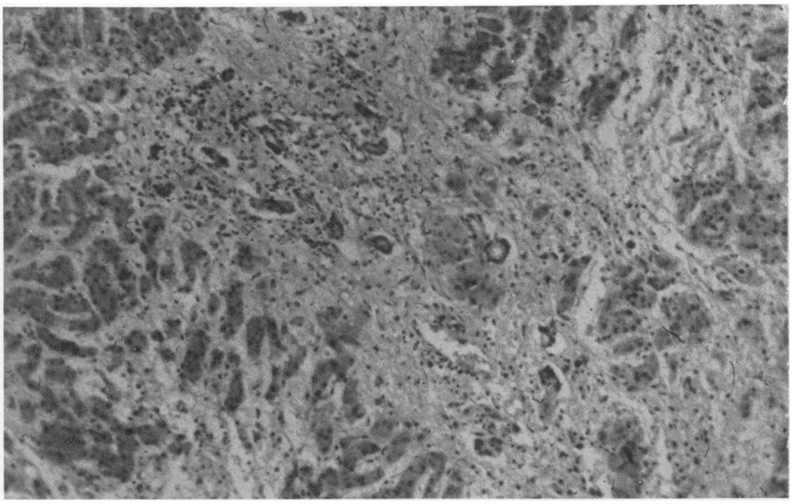
FIG. 10. Periportal inflammation and destruction of limiting plate. Hematoxylin and eosin stain. × 80.

FIG. 11. Collagenous membranes radiating from portal canal, due to inflammation. Van Gieson's stain. × 110.

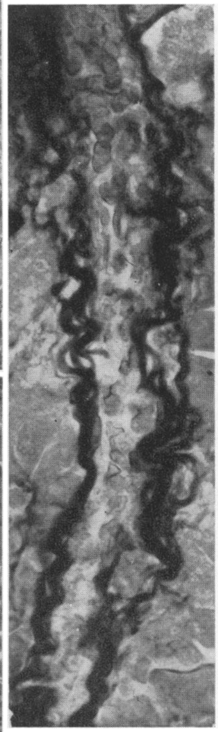
FIG. 12. Micromembranes aggregating to form membranes. Van Gieson's stain. × 550. (Reproduced by permission of the Josiah Macy, Jr. Foundation from *Transactions of the 11th Conference on Liver Injury,* 1952, page 188.)

FIG. 13. Reconstruction of septa developing by aggregation of membranes and subdividing the lobule.

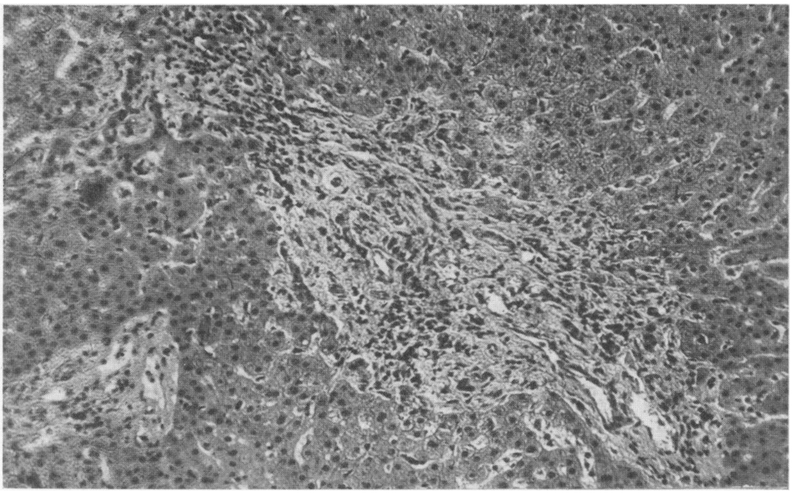
9



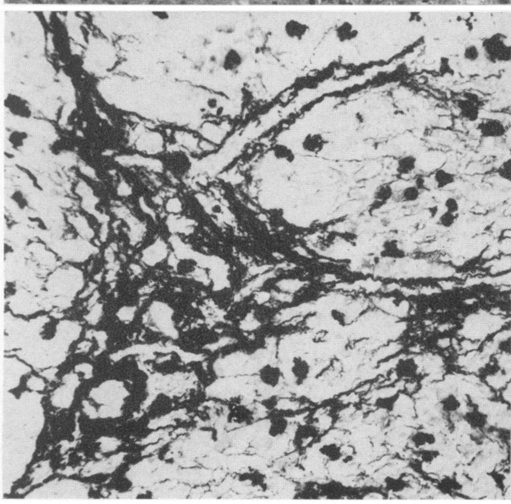
12



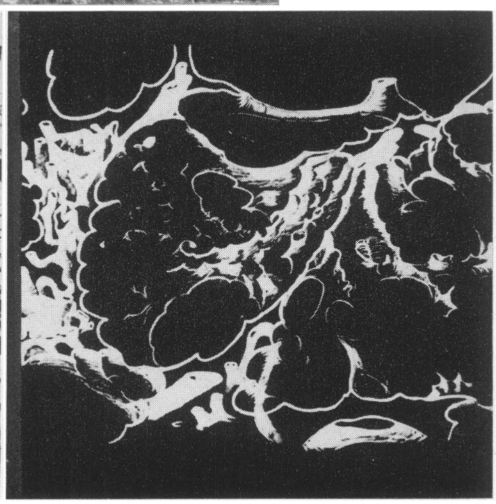
10



11



13



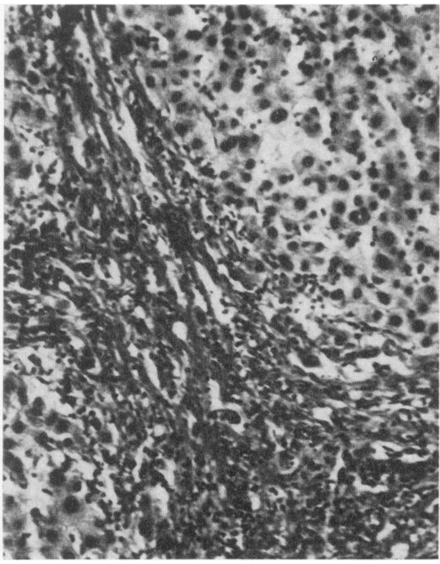
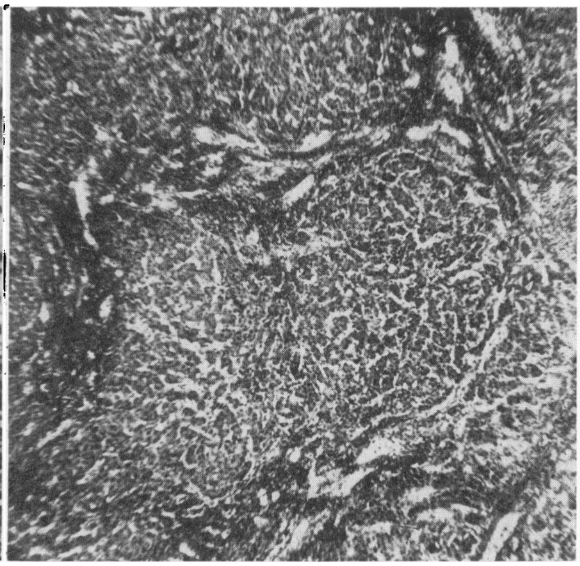
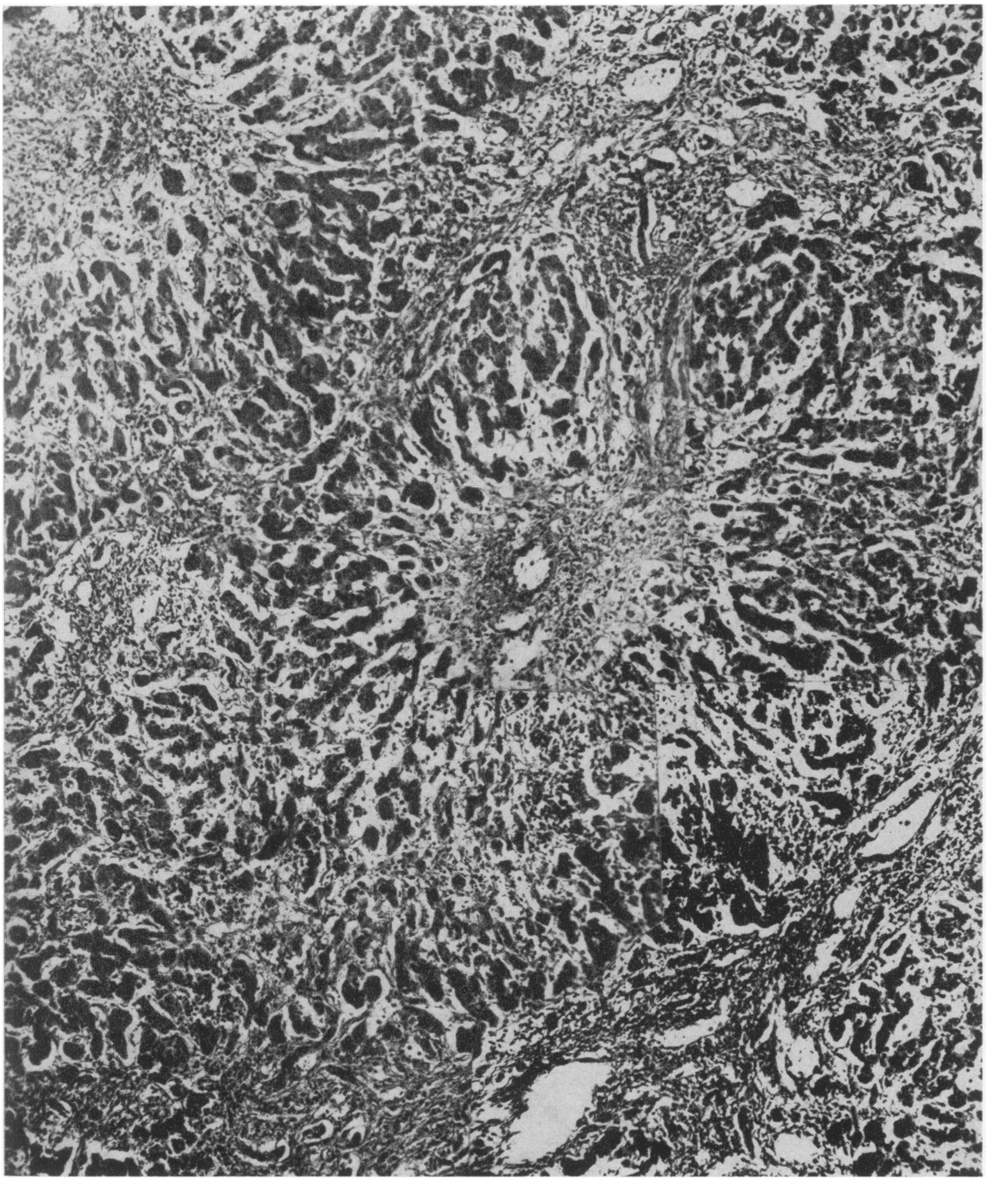
14   15

FIG. 14. Inclusion of sinusoids in developing septum. Van Gieson's stain. × 130.

FIG. 15. Connection of portal triads with each other and with central fields by septa. Van Gieson's stain. × 60.

FIG. 16. Subdivision of lobule by septa following central and periportal necrosis and membrane formation due to both chronic passive congestion and portal inflammation. A composite photomicrograph. Hematoxylin and eosin stain. × 80.



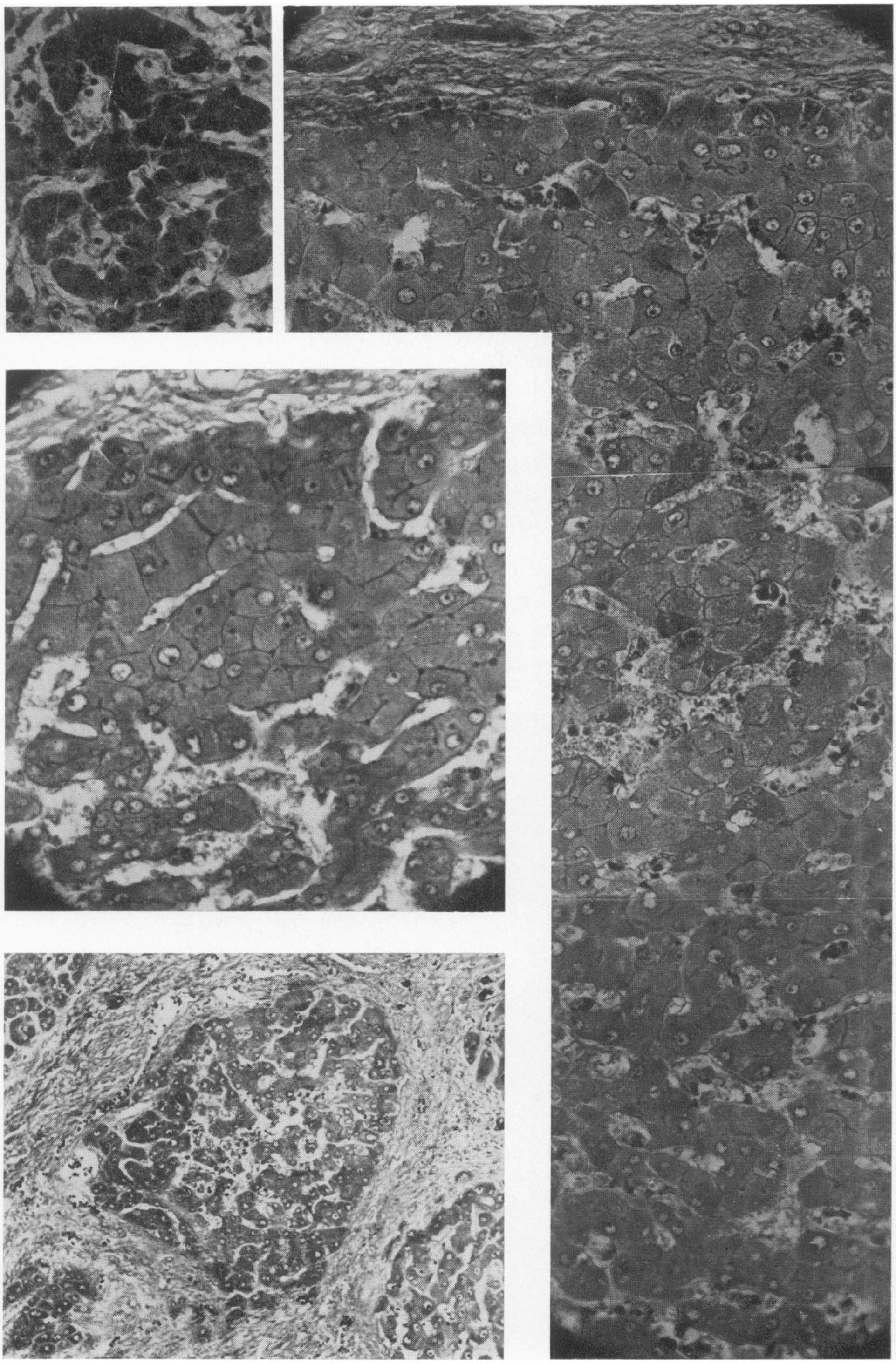
16

FIG. 17. Rearrangement of plates in lobular fragment (detail from Figure 16). Hematoxylin and eosin stain. × 280.

FIG. 18. Section from large regenerating nodule revealing liver cell plates several cells thick with amitotic division at the periphery, plates two cells thick in the intermediate zone, and plates one cell thick in the nodular center (below). Atrophic cells in surrounding septum. A composite photograph. Mallory's aniline blue stain. × 300.

FIG. 19. Same process as shown in Figure 18 in more rapidly growing nodule. Mallory's aniline blue stain. × 300.

FIG. 20. Central atrophy and necrosis in regenerated nodule. Hematoxylin and eosin stain. × 120.



17

19

20

18

FIG. 21. Isolated atrophic liver cells and regenerating liver cells in small nodules in a cirrhotic septum. Hematoxylin and eosin stain. × 80.

FIG. 22. Connection of ductule with liver cell plates. Mallory's aniline blue stain. × 300.

FIG. 23. Fissure due to stress in a fatty liver, separating two parenchymal territories with different fat content and expansion. Hematoxylin and eosin stain. × 350.

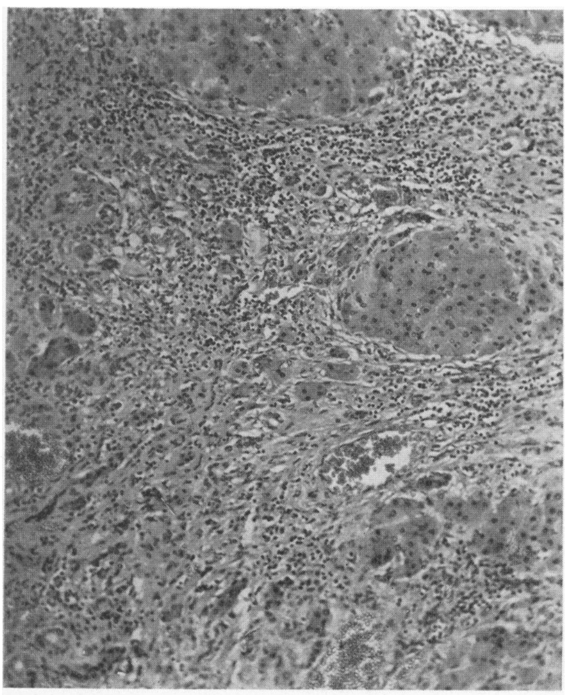
FIG. 24. Plates two cells thick with regeneration near fatty territories. Hematoxylin and eosin stain. × 230.

FIG. 25. Beginning deposition of collagenous membranes in fissure due to stress. Mallory's aniline blue stain. × 230.

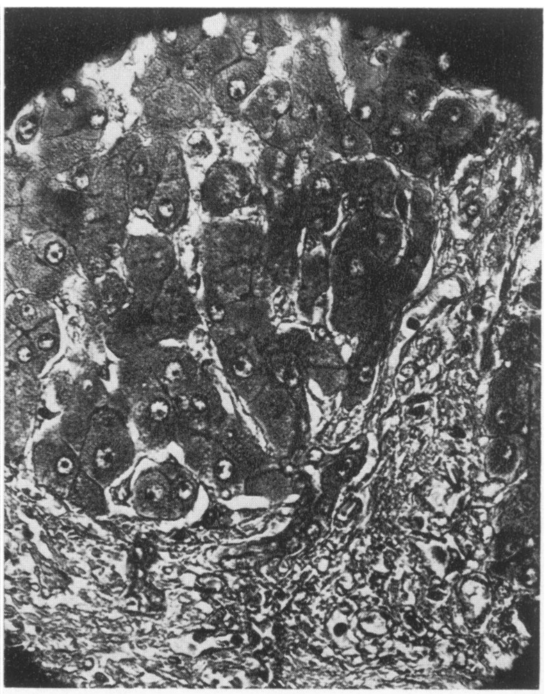
FIG. 26. Completed straight septum formed in stress fissure separating unevenly expanded lobular territories. Mallory's aniline blue stain. × 120.

FIG. 27. Fissure due to stress between regenerating and fatty hepatic territories. Hematoxylin and eosin stain. × 60.

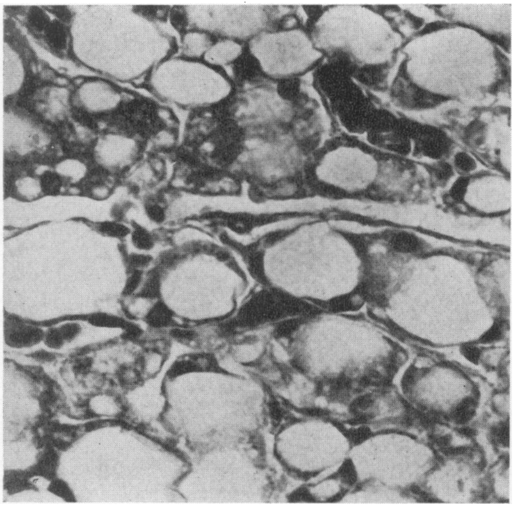
FIG. 28. Fatty cysts due to coalescence of fat droplets in several liver cells. Mallory's aniline blue stain. × 230.



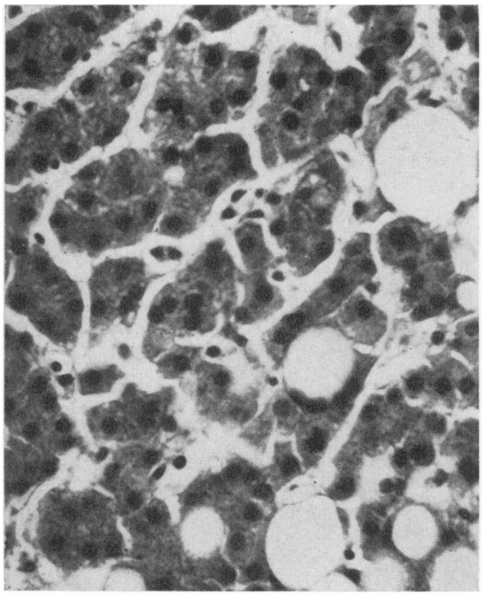
21



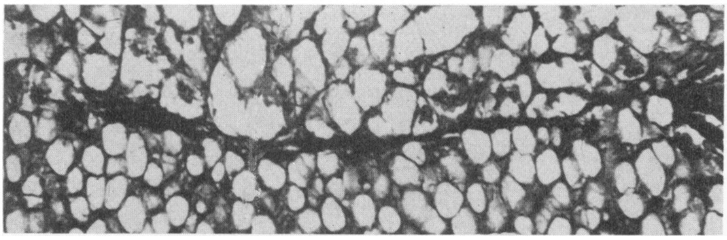
22



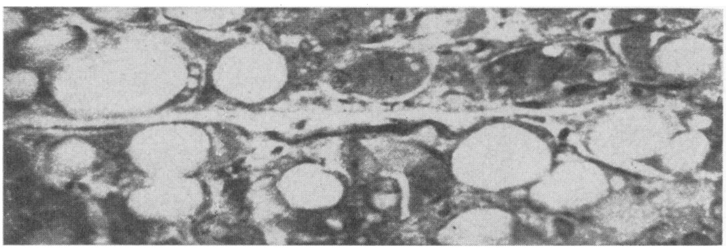
23



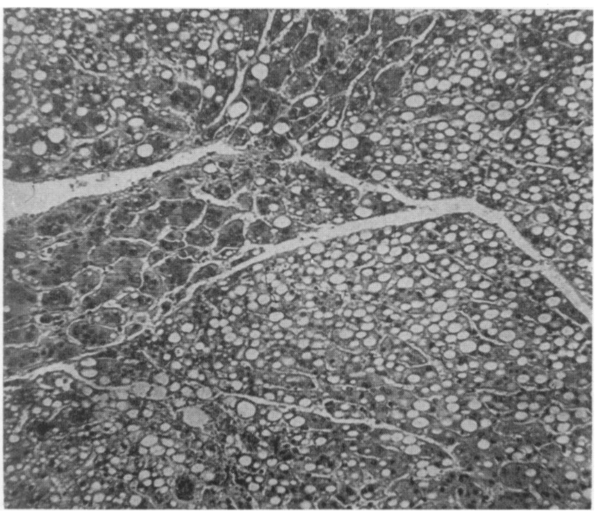
24



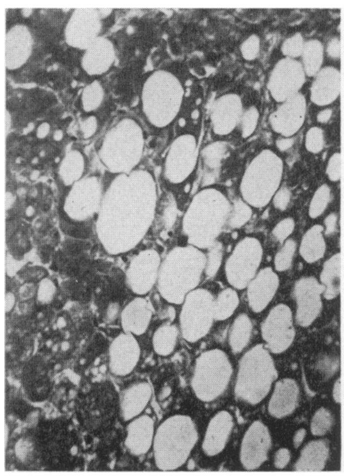
25



26



27



28

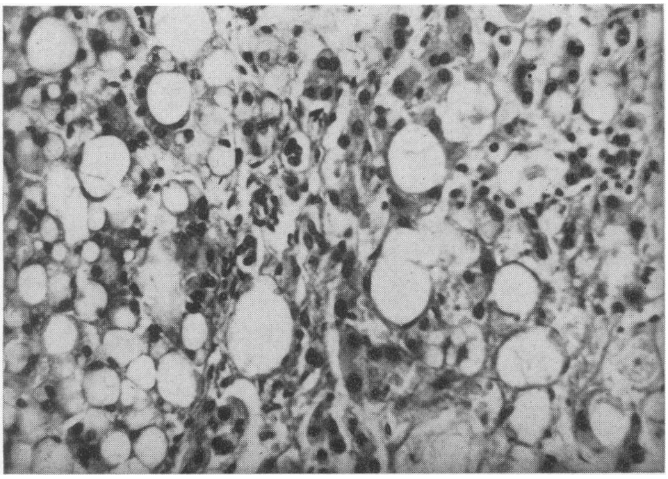
FIG. 29. Membranes developing near fatty cysts. Van Gieson's stain. × 230.

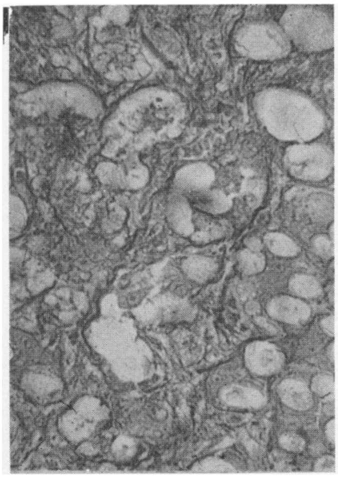
FIG. 30. Fibers developing near fatty cysts. Mallory's aniline blue stain. × 230.

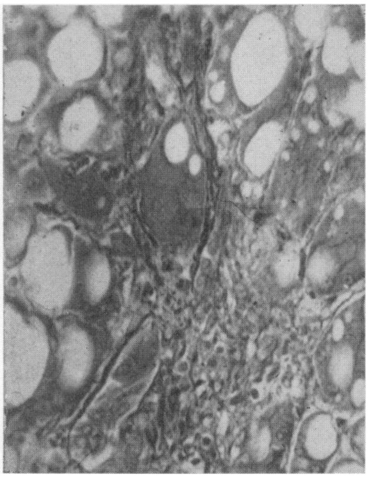
FIG. 31. Periportal radiating membranosis with septum formation following periportal inflammation with marked lipidosis. Mallory's aniline blue stain. × 60.

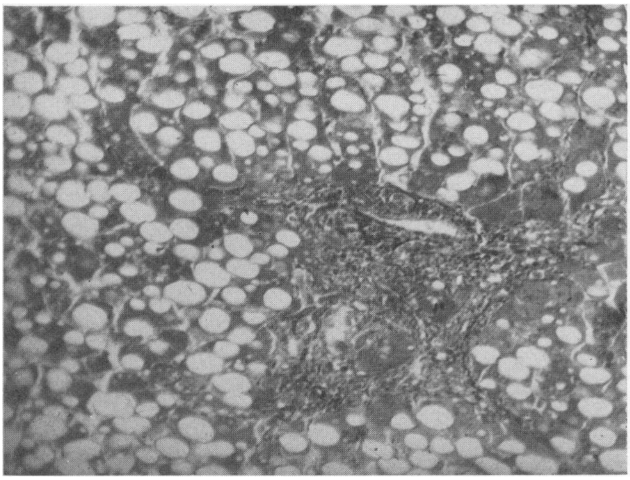
FIG. 32. Intralobular membrane formation following inflammation and necrosis associated with marked lipidosis. Mallory's aniline blue stain. × 230.

FIG. 33. Reconstruction of the connective tissue in advanced fatty cirrhosis, exhibiting the incomplete separation of the nodules. Drawn from a wax plate model by Nelson Brown.


29


30


31


32

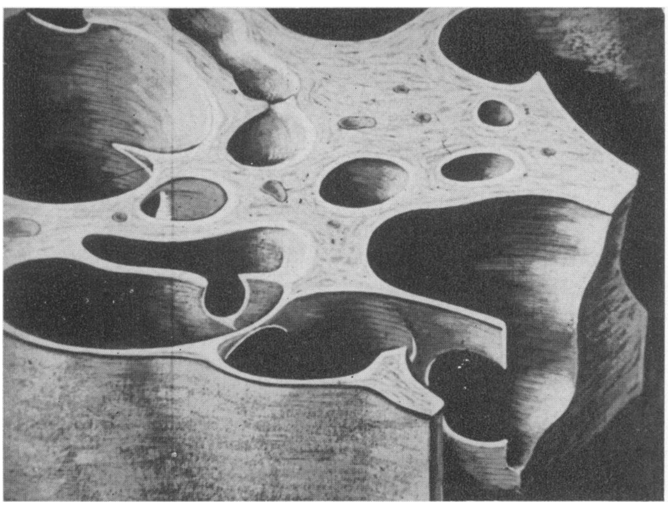

33

Fig. 34. Large intralobular bile ductule accompanied by an arteriole, both invested in a common adventitia. Hematoxylin and eosin stain. $\times$ 230.

Fig. 35. Intralobular cylindriform trabecula ensheathing ductules with pericholangiolitic inflammation. Of note is the elliptic shape of the section of the trabecula, which is different from a septum. Van Gieson's stain. $\times$ 60.

Fig. 36. Detail of Figure 24. Oblique section of cholangiolitic trabecula showing oblique and transverse sections of fibers. Van Gieson's stain. $\times$ 230.

Fig. 37. Cholangiolitic cirrhosis with maintenance of lobular architecture, the parenchyma being traversed by trabeculae. Hematoxylin and eosin stain. $\times$ 60.

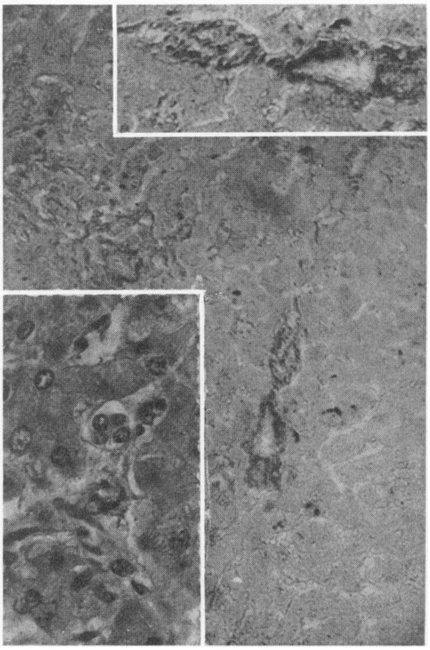
Fig. 38. Reconstruction of curved and cylindric trabeculae in cholangiolitic cirrhosis.

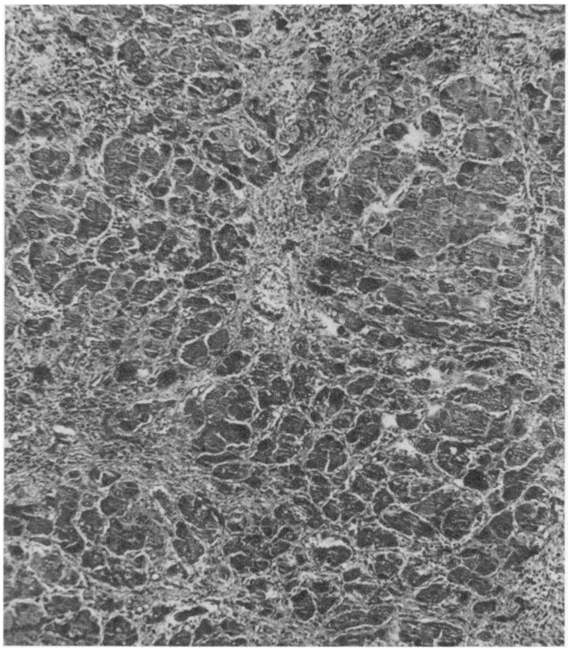
Fig. 39. Drawing showing the lobules traversed by increased and thickened cylindric trabeculae containing cholangioles. The lobular pattern is not disturbed.

36

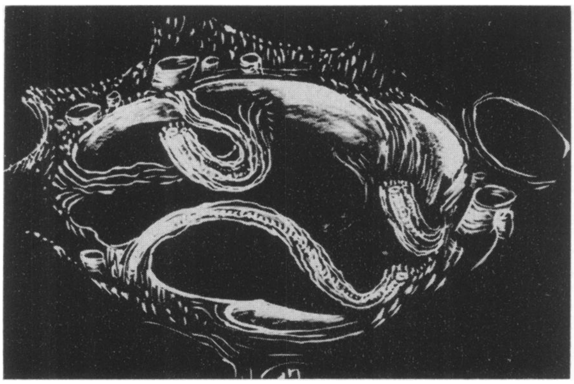
35

34

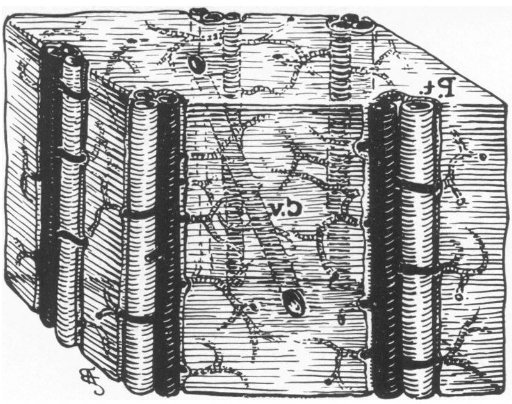




37



38



39